Does Quantitative Heterogeneity of Human Fetal Hemoglobin (Hb F) Reveal Friends or Foes of KLF1 in Globin Gene Switching ?

The chemical heterogeneity of fetal hemoglobin (Hb F) due to variable ratios of the Gγ and Aγ globin subunits reflects genetic complexity because of common dimorphisms such as Hb F Sardegna (or Aγ75(E19) Ile>Thr; also known as AγT) in Caucasians, and common variants such the Gγ globin variant, Hb F Malta I (or Gγ117(G19) His>Arg) that is in tight linkage disequilibrium with the β globin variant Hb Valletta (or β87(F3) Thr>Pro) and is found in 1.8% of neonates from Malta. Comprehensive and integrated maternal and neonatal testing has led to the finding of triple compound heterozygotes with Hb F Malta I in association with Hb F Sardegna and Hb Valletta in whom all globin genes that are functional in the transition from fetal to adult Hemoglobin profiles are genetically tagged, and quantifiable with High Performance Liquid Chromatography in the neonate or mRNA in the adult in the context of diverse XMNI –158 C>T Gγ globin and $(AT)_XT_Y$ –540 β globin haplotypes. The interaction between XMNI and $(AT)_XT_Y$ revealed "conditional" *cis-trans* interplay that appeared to be under developmental control. A family with members carrying Hb F Malta I in association with a rare form of the Hereditary Persistence of Fetal Hemoglobin has also been found. The genetic cause has been traced to haplo-insufficiency of the putative erythroid master regulator KLF1, and, as confirmed by functional assays *in vitro*. However, levels of Hb F expression varied considerably (3.3% – 19.5%) while a second family from Malta with the same *KLF1* mutation (p.K288X) had normal Hb F indicating interplay of KLF1 with modifying genes. These data, together with comparative expression profiling of human erythroid progenitors, indicated a small set of additional gene products that may interact positively (friends) or negatively (foes) at the level of commitment or expression in globin gene switching with significant effects on the

Mean Corpuscular - Hb F. Whole genome sequencing on critically informative family members currently in progress may further uncover the complex genetic interactions in developmental globin gene control.

Disclosures: No relevant conflicts of interest to declare.